EXHIBIT 2

Report of Jonathan Borak, MD, DABT

Re: Ada L. Trombley

February 14, 2019

I. Introduction

1. This report addresses issues of specific causation as they relate to the prosthetic joint infection (PJI) suffered by Ms. Ada L. Trombley following right knee arthroplasty in April 2009. I have previously provided two expert reports (the first dealing with general causation and the second with specific causation for a different plaintiff), several supplemental reports, and testimony in two depositions and a trial, all responsive to related matters. Those earlier reports and testimony, including exhibits and citations, are hereby incorporated into my current report.

2. I am Clinical Professor of Medicine at Yale University, a faculty member of the Yale Occupational and Environmental Medicine Program, and Adjunct Associate Professor of Medicine at The Johns Hopkins University. I am also President of Jonathan Borak & Company, a consulting firm in New Haven, Connecticut. I am or have been a member of numerous national advisory panels, an officer or director of numerous medical and scientific organizations, an editorial board member or peer reviewer of numerous medical and scientific journals, and the author of numerous books, book chapters and peer reviewed publications. My current CV is attached as an appendix.

II. Materials Reviewed

3. In the present matter, I was asked by Mr. Corey Gordon of Blackwell Burke to review the following medical records, expert reports, and depositions:

Ms. Trombley's medical records (listed alphabetically)

Bay Park Community Hospital
Cataract and Laser Institute
Consulting Orthopedic Associates
Mercy Cardiothoracic Surgical Associates
Mercy Health Infectious Disease
Mercy Health – West Park Family Medicine
Nephrology Associates of Toledo
Nephrology Consultants of Northwest Ohio
"Plaintiff Produced Records – Various Records"
ProMedica Laboratories
ProMedica Physicians – Beer Orthopedics
ProMedica Toledo Hospital
ProMedica Wildwood Orthopedic and Spine Hospital

Social Security Administration
The University of Toledo Medical Center
Toledo Cardiology Consultants
Toledo Clinic
Dr. John Valade
Walmart Pharmacies Corporate

Deposition transcripts (listed alphabetically)

Dr. Karl J. Beer	(01/09/2019)
Dr. Nelson Nicolasora	(01/15/2019)

Expert Reports

Eric Brown, MD	(01/19/2019)
William R. Jarvis, MD	(01/25/2019)

4. I also reviewed a large number of scientific reports related to surgical warming devices, operating room procedures, risk factors for surgical complications and infections, and other related medical and scientific issues. Specific publications are cited in this report and in my earlier reports and depositions. I have also attached a cumulative reference list of the medical and scientific literature that I have reviewed in the context of this and related matters.

5. I understand that there may be additional depositions and further discovery in this matter, and I reserve the right to amend or supplement my report in light of any additional records or evidence that become available. Likewise, the medical literature is dynamic and changing and therefore I reserve the right to amend or supplement my report in light of any additional medical or scientific evidence of which I become aware.

III. Background

6. Ms. Trombley (DOB: 12/11/48) underwent right knee arthroplasty (TKA) on 12/02/11 for treatment of degenerative joint disease. She had undergone left TKA in August, 2001 and had returned to see her orthopedist (Dr. Beer) on 10/11/11 because of severe right knee pain. The 12/02/11 anesthesia record [20BPCH-0032-34] documents that she was obese (Ht: 162 cm; BW: 96 kg; BMI: 36.6); her American Society of Anesthesiologists (ASA) score was 3; and she received 2 grams of Cefazolin (Ancef) IV as pre-operative prophylaxis. Skin prep was performed using Chloraprep® (chlorhexidine and isopropyl alcohol). Surgery lasted 71 minutes (total OR time was 127 minutes) and her core temperature was stable throughout the surgery (36-37°C). There was an apparent tourniquet dysfunction during the procedure, but no other "events" were noted. She was discharged from hospital on 12/04/11.

7. Post-operatively, Ms. Trombley was examined by Dr. Beer on 12/15/11, at which time her surgical incisions was "clean, dry and intact". He noted that she was

progressing slowly, but was "without signs of an infection" [13PPBO-00043]. She was next seen by Dr. Beer on 01/10/12 with complaints of acute onset of "increase in wound drainage and pain". Serous and purulent drainage was seen at the proximal end of the incision, the knee was swollen and infection was diagnosed. Aspiration of the joint fluid was attempted, but unsuccessful. Superficial cultures were taken from the wound. She was directed to the Toledo Hospital for admission on the following day for surgical treatment [13PPBO-00042].

8. Ms. Trombley was admitted to Toledo Hospital on 01/11/12. An infectious disease consultant noted that she had "creamy yellow fluid" draining from the incision, as well as fever and chills, an elevated WBC, ESR and CRP, and gram positive cocci in her culture [13PTH-00100]. That day, the wound was opened and found to have "a large cavity full of purulent material" [Beer depo, p.67].[1] The cavity was drained and irrigated, the prosthetic joint was removed, the bone and wound were cleaned, an antibiotic spacer was inserted, and antibiotic treatment with daptomycin was started [47PTH-00185 et seq.]. Cultures from the surgical wound documented that infection was caused by Group B streptococcus (GBS) and the antibiotic was changed to IV ceftriaxone (Rochepin), which was administered until 02/24/12 after which she began treatment with oral cephalexin (Keflex) which was continued until 04/19/12. [10JVA-00149, 151]

9. In addition to osteoarthritis and a history of prior surgery, Ms. Trombley's medical history prior to 12/11/09 was remarkable for obesity, adult-onset diabetes, anemia, hyperlipidemia, hypertension, chronic renal insufficiency and psoriatic arthritis.[2] The Walmart Pharmacy records indicate that after 2005 she was repeatedly prescribed numerous medications including a variety of antibiotics, antihypertensive agents, lipid-lowering agents, pain medications, corticosteroids, and methotrexate, [16WAL-0008 *et seq*.].

9a) Ms. Trombley had longstanding obesity. The following table indicates her body weight and body mass index (BMI) as documented in her medical records prior to her right TKA. In her pre-op assessment by Dr. Beer, her weight was noted as 96 kg, her height as 162 cm, and her calculated BMI was 36.6 [20BPCH-00209].[3] Some of the records report her measurements in metric units and other in Imperial

[1] Dr. Beer described the infection as focused superficially: "the worst part of her infection was like right in the incision, it wasn't like it was in the joint and came out" [Beer Depo p.71-2]. It is also noteworthy that the wound had been "clean, dry and intact" several weeks before, that the onset of symptoms was acute, and that Group B Strep are often associated with bacteremia. This combination of findings strongly argues that Ms. Trombley's PJI resulted from hematogenous spread.

[2] Ms. Trmbley's medical history prior to 2008 is not directly documented in the records that I reviewed. She reportedly had not seen any physicians for the six years prior to 08/04/08, when she was evaluated as a new patient at the Toledo Clinic [41UTMC-00366-370]. However, records from Walmart Pharmacy indicate that she was treated by Dr. Meredith beginning at least in late 2005 [16 WAL-00040],

[3] BMI is calculated in the metric system as [kg/m^2], with body weight in "kg" units and height in "m" units. Calculation in the Imperial system is less intuitive. It is calculated as weight in "lbs" units divided by height squared in "inch" units, all multiplied by 703. Thus in the Imperial system, BMI = [(lbs/in^2) x 703] (1).

units; the following table includes her weight measures as reported. I calculated her BMI using her height as 63" or 160 cm.[4]

Table 1: Ms. Trombley's BMI

Date	Weight (lb) (lb)	(kg)	BMI♣	Source
11/25/08	216.4		38.3	41UTMC-00361
06/18/09	205		36.3	41UTMC-00341
10/28/10	225		39.9	12SSA-00118
10/11/11	215		38.1	13PPBO-00034
10/31/11	216		38.3	10JVA-00096
11/22/11		96	37.5	20BPCH-00025, 00209
12/02/11		96	37.5	20BPCH-00209
01/11/12		92.5	36.1	1PPR-00060
29/05/12	183		32.4	13PPBO-00011
06/29/12		82.9	32.4	1PPR-00055
08/17/12		84	32.8	1PPR-00046

♣ = calculations based on height = 63" or 160 cm;

9b) Ms. Trombley had Type II (adult onset) diabetes mellitus (AODM). Her diabetes was apparently first diagnosed around 2003 and she was treated thereafter with metformin (500 mg po qam and 1000 mg qhs) and rosiglitazone (Avandia) (2 mg po) [41UTMC-00371]. By 11/22/11, when she was evaluated by Dr. Smith in anticipation of her pending TKA surgery, her diabetes was treated with metformin (1000 mg bid) and glipizide (5 mg qd) [10JVA-00165].

9c) Ms. Trombley had chronic kidney disease (CKD) that was first noted in the available records on 07/14/08, when her calculated endogenous glomerular filtration rate (GFR) was 49 [41UTMC-00382]. Renal insufficiency was also noted on 11/22/11, when she was evaluated by Dr. Smith in anticipation of her pending TKA surgery: "elevated creatinine of 1.31 milligrams/dl and a low glomerular filtration rate of 41 … Renal insufficiency" [10JVA-00165].[5] Thus, at the time of her 2011 surgery, Ms. Trombley suffered Stage 3b kidney disease (i.e., moderate-severe kidney damage).[6]

[4] There is a small amount of variability in her height as reported in various medical records. I have used 63" for BMI calculations because it is the most frequently cited and because it was adopted by Dr. Jarvis [Jarvis Report p.2].

[5] There is an apparent typo in Dr. Smith's note which states: "BUN was normal at 70 mg/dl". The actual lab report indicates that the BUN was 17 mg/dl [20BPCH-00269].

[6] Evaluating renal function by use of serum creatinine, rather than GFR, "overestimates renal function" and underestimates CKD, especially in older women (2).

The following table summarizes her renal function test results from 07/14/08 thru 09/17/12, documenting her persistent renal insufficiency. She also had persistent hyponatremia, which was apparently not evaluated clinically, but may have been secondary to renal tubular dysfunction.

Table 2: Ms. Trombley's renal function

Date	Creat	BUN	GFR	[Na+]	Osmolality	Source
07/14/08	1.2	18	49	131		41UTMC-00381, 2
08/04/11	1.1	22		135		10JVA-00120
10/31/11	1.4	19	49	131		10JVA-00096
11/22/11	1.31	17	41	132		20BPCH-00269
12/02/11	1.2	17		127		20BPCH-00021
12/04/11	1.17	21	47	127	268	20BPCH-00063, 65
01/10/12	1.30	17	41	127		47PTH-00139
04/16/12	2.75	27	17	132		49PML-00016/17
05/17/12	2.19	22	23	137		24NCNWO-00010
08/17/12	2.33	24	21	136		24NCNWO-00009
09/17/12	2.43	27	20	134		24NCNWO-00007

9d) Ms. Trombley had normochromic, normocytic anemia that was apparently first documented in 2008. The earliest complete blood count (CBC) that I found in her records (02/08/08) indicated low levels of hemoglobin (HgB = 10.5), hematocrit (Hct = 30.6), but normal levels of mean corpuscular volume (MCV = 87.2), and mean corpuscular hemoglobin (MCH = 30.0) [41UTMC-00382]. Those values are consistent with anemia resulting from chronic kidney disease (CKD), especially in a patient with both CKD and diabetes (3-7). I found no indication that the anemia was evaluated or treated at the time other than occasional iron supplementation.

The following Tables 3a and 3b summarize her hematological test results from 2008 through 09/17/12. They document persistently low HgB and HCT and normal erythrocyte indices (MCV, MCH). Her first two iron studies (8/18/11 and 11/08/11) indicated normal serum iron levels and normal total iron binding capacity, borderline low binding saturation, and normal ferritin levels. She was prescribed oral iron supplements beginning on 8/18/11 [16WAL-00049], but showed little response through 11/08/11. A small increase in HgB and a marked increase of serum iron and ferritin were noted on 11/16/11, which I presume were the results of parenteral iron supplementation, but I have not found the records for that treatment. The effect of such treatment was short-lived.

Table 3a: Ms. Trombley's hematological test results[7]

Date	HgB	HCT	RBC	MCV	MCH	RDW	Source

[7] Following are the normal ranges for these tests as reported by Bay Park Community Hospital: HgB: 11.7- 16 g/dL; HCT: 35-47; RBC: 3.80-5.20 $x10^{12}$/L; MCV: 81-100 fL; MCH: 26-33.5 pg; RDW: 11.4-14.7%.

07/14/08	10.5	30.6	3.51	87.2	30.0	13.5	41UTMC-00382
03/05/09	9.3	27.7	3.10	89.2	29.9	17.2	41UTMC-00356
10/01/09	10.9	32.3	3.68	87.9	29.7	15.1	41UTMC-00338
08/04/11	10.9	32.9	3.89	84.6	27.9	16.0	41UTMC-00319
10/31/11	10.7	31.0	3.83	81	27.9	13.5	10JVA-00117
11/08/11	11.4	34.4					47PTH-00136
11/22/11	11.9	35.2					20BPCH-00269
12/03/11	10.9	32.9	3.75	88	29.0	18.9	20BPCH-00063
12/04/11	10.3	33.5	3.77	89	29.9	18.6	20BPCH-00063
02/02/12	10.6	31.8	3.65	87	29.0	15.9	49PML-00007
09/17/12	10.0	30.0	3.41	88	29.4	14.3	24NCNWO-00007

Table 3b: Ms. Trombley's iron study results [8]

Date	Fe^+	TIBC	Fe^+/TIBC	Ferritin	
08/18/11	49	423	12	27	41UTMC-00314
11/08/11	62	361	17	36	47PTH-00136
11/16/11	430	277	155	723	47PTH-00137

In summary, Ms. Trombley's laboratory results indicate that she had anemia that was persistent and unexplained. At the time of her TKA on 12/02/11, her hemoglobin level was apparently in the normal range, presumably because she had received iron supplements shortly prior to surgery, but subsequent blood testing indicated anemia the following day and she remained anemic thereafter.

9e) Ms. Trombley used opioid medications (including oxycodone, hydrocodone, codeine and tramadol) that were prescribed almost continuously for more than two years prior to her TKA on 12/02/11 [16WAL-00043-49].

9f) Ms. Trombley had hyperlipidemia. On 07/14/08, prior to treatment, her cholesterol levels was 305 mg/dL (normal < 200) and her triglyceride level was 247 mg/dL (normal < 150) [41UTMC-00381]. She was first prescribed statin medications (e.g., pravastatin; lovastatin) beginning 08/08 with prescriptions filled by Walgreen's intermittently through 09/27/11 [16WAL-00048]. Despite use of statins, her cholesterol and triglyceride levels remained elevated.

9g) Ms. Trombley had hypertension that was first diagnosed in between 1988 and 1993 [41UTMC-00370]. At various times, she was treated with diuretics (e.g., hydrochlorothiazide, triamterene), beta-blockers (e.g., Coreg®, metoprolol), and acetyl cholinesterase (ACE) inhibitors (e.g., lisinopril).

[8] Following are the normal ranges for these tests as reported by University of Toledo Medical Center: Serum Fe: 30-160 µg/dL; TIBC (Total Iron Binding Capacity) 250-450 µg/dL; Fe^+/TIBC: 20-50%; Ferritin: 11-307 ng/mL

9h) Ms. Trombley had been diagnosed with inflammatory psoriatic arthritis, although the basis for the diagnosis is unclear in the records. Because of concern for that diagnosis, she was treated with methotrexate beginning by 11/28/08 [16WAL-00043] and with various corticosteroids (e.g., prednisone, methylprednisolone) beginning by 01/06/08 [16WAL-00008, 00045]. Prednisone was prescribed continuously on a daily basis from 03/11/10 through 12/02/11[20BPCH-00011, 00017].

9i) Ms. Trombley had a history of recurrent urinary tract infections [24-NCNWO-00005].

III. Discussion

A. Obesity and Prosthetic Joint Infections

9. Obesity is a well-established risk factor for PJI, an association that has been repeatedly and consistently documented (8). Numerous published studies have considered that association, but most have been relatively small and underpowered. Accordingly, my earlier reports focused on the results of four recent meta-analyses that aggregated the findings of those smaller studies, thus addressing concerns about limited statistical power (9-12). Those meta-analyses, conducted using appropriate and documented methods, indicated that obesity is a significant, independent risk factor for PJI and that risks increase as BMI increases over 30.[9] The meta-relative risks were generally >2, ranging up to 5.06. Stronger associations were found in the studies of higher methodological quality and those that focused on total knee and hip replacements.

10. Recent reports continue to document that pre-surgical obesity is a significant risk for PJI. Following are five examples:

10a) Tan et al 2016 (15) and Tan et al 2018 (14) reported the results of a retrospective analysis of 43,253 TJAs performed in 27,717 patients treated between 2000 and 2014 at a single university hospital. Data were obtained from an institutional database which included the patients' preexisting comorbidities. Cases included both primary and revision TJAs. All records were searched electronically and then manually. Results included unilateral risk estimates for each of 17 risk factors that were significantly associated with PJI and the weighted rankings of individual risk factors based on multivariate risk calculation, with results subjected to external validation. There were 1035 cases of confirmed PJI.

Obesity (defined as BMI > 30) was significantly associated with PJI in univariate analyses (OR: 1.49; 95% CI: 1.24-1.79). In multivariate analyses, its association with PJI was highly significant ($p < 0.001$): "It is important to note that the risk of PJI increased as the BMI either increased or decreased from a nadir at 29.3 kg/m^3".

[9] Studies that treated BMI as a continuous (rather than categorical) variable indicate that risk of PJI increased significantly in a continuous, curvilinear manner beginning at BMI of about 29-30 (13;14).

10b) Bozic 2012 (16) analyzed a 5% national sample of the Medicare database, considering relative risk of PJI after 30 days post-operative in 40,919 patients who underwent primary THA between 1998 and 2007. PJI was identified as "ICD-9-CM diagnosis code 996.66 (infection resulting from an internal joint prosthesis)". Obesity and other pre-operative comorbid conditions were compiled from diagnoses (based on ICD9 codes) included in either Part A (inpatient) or Part B (outpatient) claims submitted during the twelve-month period prior to the THA. Analyses were adjusted for multiple comparisons.

Multivariate analyses were performed that included 29 comorbid conditions as well as age, sex and race. For obesity, the unadjusted relative risk was 1.97 (95% CI: 1.57-2.48) and the adjusted risk was 1.73 (95% CI: 1.35- 2.22). These results were highly significant (adjusted $p = 0.0014$).

10c) Bozic et al. 2012 (17) performed a similar analysis that focused on 83,011 patients who underwent primary TKA. Obesity and other pre-operative comorbid conditions were compiled from diagnoses (based on ICD9 codes) included in either Part A (inpatient) or Part B (outpatient) claims submitted during the twelve-month period prior to the TKA. Analyses were adjusted for multiple comparisons.

Obesity was a significant independent risk factor for PJI. The unadjusted relative risk was 1.38 (95% CI: 1.19-1.59) and the adjusted risk was 1.22 (95% CI: 1.03-1.44). These results were statistically significant (adjusted $p = 0.0219$).

10d) Lenguerrand et al 2018 (18) analyzed the National Joint Registry for England and Wales, Northern Ireland and the Isle of Man between 04/01/03 and 12/31/13. They focused on the risks of revision for PJI after THA. There were a total 623,253 THA patients followed-up for at least one year. Surgical revision for PJI was performed in 2,705 patients. Comorbid conditions and other risk factors were obtained from linked national medical and hospital databases.

Univariate and multivariate analyses were performed including age, sex, ethnicity, and more than 20 comorbid factors. Compared to those with BMI <25, risk of PJI in patients with BMI ≥ 30 was significantly increased ($p < 0.05$) with a two-fold increase in the incidence rate per thousand person-years (1.82 vs. 0.91; $p < 0.05$).

10e) Bell 2018 (19) analyzed the risks of PJI in 23,754 patients who underwent TJA between 1/1/05 and 1/31/17 at the same university hospital studied by Tan et al (14). The overall PJI rate was 0.98%. Univariate and multivariate analyses were performed that included age, sex, race and a large number of comorbid conditions. Obesity was defined as BMI >30 and PJI was defined by the "Musculoskeletal Infection Society criteria for PJI". The association between obesity and PJI was highly significant (adjusted OR: 1.58; 95% CI: 1.19-2.08; p <0.001).

11. As discussed in my earlier reports and depositions, obesity has also been shown to be a significant risk factor for post-operative surgical infections across a variety of surgical procedures not necessarily involving the implantation of orthopedic appliances.

B. Diabetes and Prosthetic Joint Infections

12. Diabetes mellitus, both Type I and Type II, is a well-established risk factor for PJI, an association that has been repeatedly and consistently documented (8).

12a) Yang et al (20) performed a meta-analysis of 14 studies published during 1996-2014 that evaluated risks of surgical infections following TKA in diabetics. Eight studies (110,923 patients) specifically considered "deep infections". Type and severity of diabetes was not determined. The risk of PJI in diabetics was significantly increased compared to non-diabetics (OR: 1.61; 95% CI: 1.38-1.88, $p<0.001$).

12b) SooHoo et al (21) used multivariate logistic regression to analyze discharge data from 138,399 California patients who had undergone THA from 1995 to 2005. They focused on PJI documented during the first 90 days post-op and evaluated their association with preoperative risk factors, including diabetes. Diabetics were grouped into those with complicated or uncomplicated disease.[10] Compared to patients without diabetes, risks of PJI were significantly increased in both complicated diabetes (OR: 1.94; 95% CI: 1.49-2.53, $p<0.001$) and uncomplicated diabetes (OR: 1.31; 95% CI: 1.19-1.44, $p<0.001$).

12c) Jåmsen et al (22) evaluated 7181 patients who underwent TKA and THA at a Finish hospital between 2002 and 2008. They focused on "periprosthetic joint infections" (PJI), including both deep incisional infections and "organ or space" infections that occurred within one year of surgery. Patients with diabetes were identified in the registries of the Social Insurance Institution of Finland. Analysis by logistic regression found that preoperative diabetes was associated with significantly increased risks of PJI in both univariate (OR: 3.32; 95% CI: 1.82-6.08) and multivariate (OR: 2.31, 95% CI: 1.12-4.72) analyses.

12d) Pedersen et al (23) evaluated the effect of diabetes on the risk of surgical revision for PJI following THA in 57,575 patients between 1996 and 2005 at 45 Danish hospitals. Diabetes was identified using Danish national data registries for patients including those who had received "at least one prescription for … an oral antidiabetic drug for at least one year". Within two years of surgery, the relative risk for revision due to infection was significantly increased (RR; 1.49; 95% CI: 1.02-2.19) for diabetic patients compared to nondiabetics.

[10] "Complicated diabetes is defined as diabetes associated with end-organ damage; uncomplicated diabetes was noted in 8%, whereas less than 1% of patients had complicated diabetes." (21)

12e) Iorio et al (24) compared the risks of PJI in 3468 patients with or without diabetes who underwent 4241 primary or revision TKA or THA procedures at a single hospital during 2004-2009. Diabetes was identified in the hospital records or in the hospital's aggregate databases. Risk of PJI was significantly increased in the diabetic patients (2.6% vs. 0.49%, $p<0.001$).

12f) Lenguerrand et al 2018 (18) analyzed the National Joint Registry for England and Wales, Northern Ireland and the Isle of Man between 04/01/03 and 12/31/13. They focused on the risks of revision for PJI after THA. There were a total 623,253 THA patients followed-up for at least one year. Surgical revision for PJI was performed in 2,705 patients. Comorbid conditions and other risk factors were obtained from linked national medical and hospital databases.

Univariate and multivariate analyses were performed including age, sex, ethnicity, and more than 20 comorbid factors. Patients with a pre-operative diagnosis of diabetes had a significantly increased incidence of surgical revision for PJI as compared to those without such history (1.37 vs. 0.96, $p< 0.05$).

12g) Tan et al 2016 (15) and Tan et al 2018 (14) reported the results of a retrospective analysis of 43,253 TJAs performed in 27,717 patients treated between 2000 and 2014 at a single university hospital. Data were obtained from an institutional database which included the patients' preexisting comorbidities. Cases included both primary and revision TJAs. All records were searched electronically and then manually. Results included unilateral risk estimates for each of 17 risk factors that were significantly associated with PJI and also the weighted ranking of individual risk factors based on a multivariate risk calculation, with results subjected to external validation. There were 1035 cases of confirmed PJI.

Diabetes was significantly associated with PJI in univariate analyses (OR: 2.00; 95% CI: 1.71-2.32). In the multivariate analysis, its association with PJI was highly significant ($p < 0.0001$).

12h) Bozic et al. 2012 (16) analyzed a 5% national sample of the Medicare database, considering relative risk of PJI after 30 days post-operative in 40,919 patients who underwent primary THA between 1998 and 2007. PJI was identified as "ICD-9-CM diagnosis code 996.66 (infection resulting from an internal joint prosthesis)". Pre-operative anemia and other comorbid conditions were compiled from diagnoses (based on ICD9 codes) included in either Part A (inpatient) or Part B (outpatient) claims submitted during the twelve-month period prior to the THA. Analyses were adjusted for multiple comparisons.

Multivariate analyses were performed that included 29 comorbid conditions as well as age, sex and race. For diabetes, the unadjusted relative risk was 1.46 (95% CI: 1.27-1.68) and the adjusted risk was 1.31 (95% CI: 1.12- 1.53). These results were statistically significant (adjusted $p = 0.0347$).

12i) Bozic et al. 2012 (17) performed a similar analysis that focused on 83,011 patients who underwent primary TKA. Diabetes was identified in diagnoses (based on ICD9 codes) included in either Part A (inpatient) or Part B (outpatient) claims submitted during the twelve-month period prior to the TKA. Analyses were adjusted for multiple comparisons.

Diabetes was a significant independent risk factor for PJI. The unadjusted relative risk was 1.28 (95% CI: 1.17-1.40) and the adjusted risk was 1.19 (95% CI: 1.06-1.34). These results were statistically significant (adjusted $p = 0.0025$).

12j) Kunstor et al. (12) performed a meta-analysis of 66 studies that considered post-operative complications after joint replacement surgery: the majority was total hip or knee arthroplasty. Studies were longitudinal with at least one year of follow-up after surgery. There were a total of 512,508 cases including 8026 PJIs. Twenty-three were prospective cohort studies and 43 were retrospective, either cohort or case-control studies. PJIs and superficial SSIs were analyzed separately.

The association of diabetes and PJI was reported in 29 studies, which included 210,067 arthroplasties and 3,503 PJIs. The risk of PJI was significantly increased in the diabetics (RR: 1.74; 95% CI: 1.45-2.09).

13. Numerous studies have found that there is little or no difference in the risks of PJI in patients with "well controlled" vs. "uncontrolled" diabetes. Studies have compared diabetics with and without end organ damage, or by evaluating risks according to blood glucose or HgbA1c levels.[11]

13a) As noted above, SooHoo et al (21) focused on PJI documented during the first 90 days post-op in 138,399 California THA cases. Uncontrolled diabetes was defined by the presence of end organ disease. Compared to patients without diabetes, risks of PJI were significantly increased in both complicated diabetes (OR: 1.94; 95% CI: 1.49-2.53, $p<0.001$) and uncomplicated diabetes (OR: 1.31; 95% CI: 1.19-1.44, $p<0.001$).

13b) As discussed above, Iorio et al (24) compared the risks of PJI in 3468 patients with or without diabetes who underwent 4241 primary or revision TKA or THA procedures. Risk of PJI was significantly increased in diabetic patients. For all SSI, there was no statistical difference found between "well-controlled" and "poorly controlled" diabetics as categorized by pre-operative HgbA1c levels <7% vs. >7%.

[11] Diabetes can be diagnosed based on blood glucose or HgbA1C level. Blood glucose reflects a short time window (i.e., minutes or hours) and can fluctuate greatly, while HgbA1c reflects average blood glucose over the prior 2 to 3 months and tends not to fluctuate. American Diabetes Association guidelines consider Hgb1Ac >6.5% to be diagnostic of diabetes (25). Generally, poor diabetes control is associated with higher levels of HgbA1c. Some researchers have divided the diabetes population into controlled and uncontrolled based on HgbA1c <7% or >7%.

13c) Harris et al (26) evaluated 6088 diabetic Veterans Health Administration (VA) patients who underwent TKA or THA for osteoarthritis during 2006-2009. Study patients had been diagnosed "in any encounter" during the year prior to surgery and had had at least one HgbA1c during that year. PJI ("deep wound infections") within 30 days of surgery were noted in 0.6% of the diabetic patients. There was no difference in the risks of PJI in diabetics with HbgA1c <7% vs. ≥7%.

13d) Chrastil et al (27) evaluated the risks of PJI in13,272 VA patients who had undergone TKA or THA during 2001-2011 at any of 153 VA hospitals. Patients were included if they had been diagnosed with diabetes prior to the surgery, had at least one HgbA1c during the six months prior or seven days following surgery, and had been followed post-op for at least 2 years. The diabetics were characterized as controlled or uncontrolled based on HgbA1c <7 or ≥7%. There was "no difference (p=0.86) when comparing the rate of PJI in the well-controlled diabetic patients (2.5%) and the rate of PJI in the poorly controlled diabetic patients (2.6%)".

13e) Kremers et al (28) evaluated the associations between PJI and diabetes, blood glucose levels, and Hgb1A1c in 20,171 patients who underwent TKA (10,451) or THA (9720) between 2002 and 2009 at the Mayo Clinic. Diabetes was determined using administrative and hospital databases; diabetics were included if they had a blood glucose and HgbA1c within one week of surgery. Post-op SSIs were limited to those occurring within one year of surgery. There were 192 deep tissue infections and 176 superficial infections.

Adjusted for age and gender, diabetes was significantly associated with risk of infection (HR: 1.55, 95% CI: 1.11-2.16). In general, level of blood glucose was "not significantly associated with developing PJIs". Likewise, among diabetic patients, "poor glycemic control (as assessed by HbA1c levels) was not a good discriminator of PJI risk".

14. There are also numerous reports documenting that diabetes is a highly significant risk factor for infection cause by GBS, with relative risks increased up to 10-fold compared to non-diabetics (29-33). Moreover, GBS infections were reported in nearly equal numbers of diabetics who did and did not require insulin (30).

C. <u>Anemia and Prosthetic Joint Infections</u>

15. Anemia, both pre- and post-operative, is recognized as an independent risk factor for complications, mortality and quality of life following orthopedic and other surgical procedures (34-36). The presence of pre-operative anemia has been consistently associated with significantly increased risk of PJI in TJA patients (8).

15a) Greenky et al. 2012 (37) evaluated the records of 15,222 patients who underwent TJA between 1/00 and 6/07 treated at a single university hospital. Those with acute trauma or known PJI were excluded. Patients were followed for at least 3 years post-operatively. Anemia was diagnosed by CBC testing 3-6 weeks pre-

operatively; anemia was defined as Hgb <12 g/dL in women and Hgb <13 g/dL in men. There were 2,991 with anemia and 12,231 without.

Risk of PJI was significantly greater in anemic patients (4.3% vs. 2%; p<0.01). In multivariate analyses, risk of PJI was significantly greater in those with anemia (OR, 1.88; 95% CI, 1.38–2.56; p < 0.001). Fully-adjusted multivariate analysis found even greater risk in anemic patients (OR, 1.95; 95% CI, 1.41–2.69; p <0.001).

15b) Tan et al 2016 (15) and Tan et al 2018 (14) reported the results of a retrospective analysis of TJAs performed in 27,717 patients treated between 2000 and 2014 at the same hospital. Data were obtained from an institutional database which included the patients' preexisting comorbidities. Cases included both primary and revision TJAs. All records were searched electronically and then manually. Results included unilateral risk estimates for each of 17 risk factors that were significantly associated with PJI and also the weighted ranking of individual risk factors based on a multivariate risk calculation, with results subjected to external validation. There were 1035 cases of confirmed PJI.

Iron deficiency anemia was significantly associated with PJI in univariate analyses (OR: 1.74; 95% CI: 1.48-2.05). In the multivariate analysis, its association with PJI was highly significant ($p < 0.0001$).

15c) Bozic et al. 2012 (16) analyzed a 5% national sample of the Medicare database, considering relative risk of PJI after 30 days post-operative in 40,919 patients who underwent primary THA between 1998 and 2007. PJI was identified as "ICD-9-CM diagnosis code 996.66 (infection resulting from an internal joint prosthesis)". Pre-operative anemia and other comorbid conditions were compiled from diagnoses (based on ICD9 codes) included in either Part A (inpatient) or Part B (outpatient) claims submitted during the twelve-month period prior to the THA. Analyses were adjusted for multiple comparisons.

Multivariate analyses were performed that included 29 comorbid conditions as well as age, sex and race. For anemia, the unadjusted relative risk was 1.61 (95% CI: 1.37-1.90) and the adjusted risk was 1.36 (95% CI: 1.15- 1.62). These results were statistically significant (adjusted $p = 0.0347$).

15d) Bozic et al. 2012 (17) performed a similar analysis that focused on 83,011 patients who underwent primary TKA. Pre-operative anemia was identified in diagnoses (based on ICD9 codes) included in either Part A (inpatient) or Part B (outpatient) claims submitted during the twelve-month period prior to the TKA. Analyses were adjusted for multiple comparisons.

Anemia was a significant independent risk factor for PJI. The unadjusted relative risk was 1.39 (95% CI: 1.23-1.58) and the adjusted risk was 1.26 (95% CI: 1.09-1.45). These results were statistically significant (adjusted $p = 0.0013$).

I am not aware of any evidence that short-term correction of anemia (e.g., short-term administration of iron or red blood cell transfusion to optimize blood count) normalizes the anemia-associated risks of post-operative infection.

D. Chronic Kidney Disease and Prosthetic Joint Infections

16. Chronic kidney disease (CKD) has been significantly associated with increased risk of PJI in many, but not all studies. For example:

16a) Bozic et al. 2012 (17) evaluated 83,011 Medicare patients who underwent primary TKA (details discussed above). A history of renal disease was significantly associated with increased risk of PJI (adjusted H: 1.38, 95% CI: 1.11-1.71; p = 0.0038).

16b) Bozic et al. 2012 (16) analyzed 40,919 Medicare patients who underwent primary THA (details discussed above). A history of renal disease was significantly increased in univariate analysis (RR: 1.45; 95%CI: 1.09-1.93), and increased non-significantly in multivariate analyses (RR: 1.19; 95% CI: 0.86-1.65).

16c) Tan et al 2016 (15) and Tan et al 2018 (14) reported the results of a retrospective analysis of TJAs performed in 27,717 patients (details discussed above). A history of renal disease was highly and significantly associated with risk of PJI (OR: 4.63; 95%CI: 3.50-6.04; p<0.0001).

16d) Tan et al 2016 (38) evaluated risks of PJI in 12,308 TJA patients treated between 2008 and 2013. Among those patients, they identified those with CKD Stage ≥3, however the actual number of such patients was not described. The study found a "clear linear relationship between eGFR and rate of PJI", indicating a significant association between CKD and post-operative deep infection. Infection rates and relative risks were not described for CKD patients.

16e) Deegan et al 2014 (39) evaluated outcomes of TJA in patients with mild to moderate-severe CKD (Stages 1-3). They reported that "the overall incidence of infection was rather high in the study population (3.5%)", but comparisons were not made to a matched population of normal patients.

16f) McCleery et al 2010 (40) evaluated rates of infection following TKA in Scottish patients with CKD compared to patients without kidney disease. There were 59,288 TKA patients treated during 1985-2008, including 3718 with CKD of whom 162 were receiving dialysis. Patients with CKD had significantly increased rates of early (≤90 days) infections (RR: 1.52; p=0.002) and late (>90 days) infections (RR: 4.40; p<0.001). Increased risk was noted in all CKD patients except those who underwent dialysis prior to surgery.

16g) Erkocak et al. 2016 (41) addressed "conflicting results regarding TJA in patients with chronic renal disease." Among 29,389 TJAs at a single hospital, they

identified 359 with CKD who were compared to 718 non-CKD TJA patients. Severity of CKD could not be determined, but cases were grouped as dialysis (n=50) and non-dialysis (n=319). The risk of deep-tissue PJI was significantly increased in the CKD dialysis patients (p<0.01), but not in the non-dialysis CKD patients.

16h) Miric et al 2014 (42) evaluated perioperative morbidity in 41,852 TKA patients in a TJA registry, of whom 2686 had CKD. CKD patients were grouped according to stage of disease (3-5). There were 297 PJIs ("deep SSIs") during the first year after surgery. The risk of PJI in CKD patients was marginally increased (0.89% vs. 0.70%) compared to patients without CKD, but the increases were not statistically significant.

16g) The Second International Consensus Meeting on Musculoskeletal Infection (ICM-2) concluded that a history of renal disease is a "Strong" risk factor for PJI, with an agreement consensus of 98% (8) .

E. Opioid Use and Prosthetic Joint Infections

17. Opioids can interfere with several aspects of normal immune system function (43-45); the mechanisms underlying these effects are not well understood. In animal studies, pretreatment with opioids predisposes to surgical infections, sepsis and mortality. Although less well researched, there are concerns that similar effects could be seen in humans.

Because of such concerns, the risks of PJI associated with preoperative use of opioids have been recently studied by analysis of hospital and health system databases. To understand these studies, it is necessary to appreciate that a diagnosis of "opioid abuse" does not necessarily imply either dependency or addiction. Likewise, that diagnosis does not imply parenteral (e.g., intravenous or IV) use of prescription or illicit drugs. There are separate ICD9 codes for "opiate dependency" and "nondependent opioid abuse", but the distinction is often difficult and the two are sometimes combined for research purposes:

> "… as it often is difficult to distinguish between opioid abuse and dependence in the hospital setting, we decided to combine the two entities for the primary analysis - an approach that is consistent with the definition of ''opioid use disorder'' in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)" (46).

18. Following are summaries of recent studies that demonstrate a significant association between opioid use and PJI.

18a) Memendez et al 2015 (46) performed a retrospective analysis of the Nationwide Inpatient Sample from 2002-2011, a dataset that is maintained by the US Agency for Health Care Research and Quality. The dataset, a 20% stratified sample of discharges from 1000 hospitals, included 9,307,348 hospitalizations for

"major elective orthopedic surgery". Among those patients 15,901 (0.2%) were diagnosed as opioid abuse or opioid dependence.

Surgical site infections, including PJI, were very significantly associated with opioid abuse: unadjusted OR: 3.4 (95% CI: 2.8-4.1; p <0.001); fully-adjusted OR 3.2 (95% CI: 2.6-3.9; p <0.001).

18b) Cozowicz et al 2017 (47) analyzed the Premier Perspective database which contains data from ≈ 25% of US hospital discharges 2006-2013, including 1,035,578 elective THAs and TKAs. The primary effect variable was "opioid utilization, defined as perioperative in-hospital opioid prescription" on the day of surgery or the following day. Patients were categorized in quartiles according to their calculated morphine equivalent opioid doses.

Compared to patients in the lowest three quartile categories, those in the highest opioid category had significantly increased risk of postoperative surgical infection (OR: 1.485; 95% CI: 1.236-1.784; p < 0.001).

18c) Bell et al 2018 (19) analyzed the risks of PJI in 23,754 patients who underwent TJA between 1/1/05 and 1/31/17 at a single university hospital. The overall PJI rate was 0.98%. Univariate and multivariate analyses were performed that included age, sex, race and a large number of comorbid conditions. Opioid users were identified as "those who were currently taking opioids at the last outpatient visit before surgery or during preadmission testing, as noted in the records." There were 5051 patients who were opioid users and 18703 who were opioid naïve.

The rate of PJI was significantly increased in the opioid users (1.4%; 71/5051) compared to the opioid naïve patients (0.86%; 162/18,703). When adjusted for potential confounders using multivariate analysis, opioid usage remained a significantly increased independent risk factor for development of PJI within 2 years post-operatively (adjusted OR, 1.53; 95% CI, 1.14-2.05; p = 0.005).

18d) Cancienne et al. 2018 (48) performed a retrospective analysis of the PearlDiver medical records database from 1/1/07 to 4/1/16. This database, which combines data from Humana and Medicare using ICD9 diagnostic codes and CPT procedural codes, contains about 20 million patients with orthopedic diagnoses. There were 113,337 primary TKA patients with at least 6 months of post-operative follow-up. Preoperative opioid users were defined as "those filling at least one narcotic prescription between 4 months and 1 month prior to the date of TKA". The number of filled narcotic prescriptions during this time was "obtained and divided into 1, 2, 3, or ≥4 preoperative filled prescriptions in the 3-month preoperative time window".

The risk of PJI during the first post-operative year increased with increasing number of narcotic prescriptions. Overall, preoperative narcotic use was very significantly

associated with increased risk of PJI within 1 year (OR 1.16; 95% CI: 1.11-1.22; $p <$ .0001).

18e) Tan et al 2016 (15) and Tan et al 2018 (14) reported the results of a retrospective analysis of 43,253 TJAs performed in 27,717 patients treated at a single university hospital between 2000 and 2014. Data were obtained from an institutional database which included the patients' preexisting comorbidities. "Drug abuse" was defined as "any patient with a history or current use, with recent or current use considered an absolute contraindication to elective surgery". There were 1035 cases of confirmed PJI. Drug abuse was the most significant individual comorbid risk factor (OR: 6.53; 95% CI: 2.76-13.86). In multivariate analysis, its association with PJI was highly significant ($p = 0.0003$).

F. Cumulative Risk Factors and Prosthetic Joint Infections

19. The above sections of this report considered the evidence linking several individual comorbid conditions with an increased risk of PJI. That approach assumes that it is possible to isolate the contributions of individual risk factors. However, it seems more probable that infection results from multiple factors. This is reflected in statements from two expert orthopedic surgeons, Dr. Mike Reed and Dr. Karl Beer.

19a) Dr. Reed, senior author of the McGovern study on which Dr. Jarvis relied, has written that almost all surgical wounds are contaminated at the time of surgery: "It is likely that almost all surgical wounds are contaminated …" (49).[12] Because PJIs are generally reported in fewer than 2% of patients, it follows that whether a given surgical wound develops infection will depend on a variety of factors (i.e., "multiple reasons"), not simply the possibility of wound contamination.

19b) Dr. Beers, during his deposition, was asked about Ms. Trombley's risks of surgical complication. He testified that PJI was her major risk ("primarily it's infection"), which was "most likely" because of multiple risk factors:

> "A. And it's also in her particular case because of her risk factors it was the most likely thing to happen.
> Q Okay. And so what were her risk factors that you just referenced?
> A Um, well, she's type 2 diabetic.
> Q Okay.
> A She's obese.
> Q Okay.
> A She had hypertension. She had renal insufficiency. She was on chronic steroids, Prednisone. And somebody said that part of her arthritis problem was psoriatic arthritis, which is an immune compromised type of arthritis.

[12] The almost universal prevalence of surgical wound contamination has been observed more generally. For example: "In clean surgery, the wound is often contaminated at closure. The proportion of contaminated wounds in cardiac surgery can be as high as 89%, depending on the type of surgery and the microorganism" (50).

Q That's actually in the medical record, correct?
A Yes." [Beers depo 23-4]

Accordingly, surgical researchers have considered ways to evaluate and quantify such multiple risks. For example, consider the following:

> "… considerable effort has been made in the past decade to identify risk factors for PJI. Although both modifiable and non-modifiable risk factors have been identified, few studies have effectively reconciled the relative influences of such factors. An effective, validated preoperative tool to quantify the risk of PJI could potentially allow surgeons to intervene before, or even to avoid, operating on individuals for whom the risk of PJI may outweigh the potential benefits of TJA". (14)

> "Multiple clinical risk-stratification classification systems … have been shown to correlate with the risk of morbidity and mortality in surgical patients… Our study builds on the findings of previous investigators by identifying the specific comorbidities associated with periprosthetic joint infection and with postoperative mortality, thus providing a more clinically meaningful basis for communication between surgeons and patients and for clinical decision-making." (16)

20. To illustrate the use of such a risk calculator for PJI, I accessed the Total Joint Replacement Risk Calculator (TJRRC) available from the American Joint Replacement Registry, a part of the American Academy of Orthopedic Surgeons Registry Program.[13] The TJRCC was developed using Medicare data. Ms. Trombley was determined to be disabled and eligible for Medicare beginning 08/11, although she was not yet 65 years of age [12SSA-00002-3; 17SSA-00138-9]. Because of her age, it is uncertain whether she would have been included in the Medicare cohort, thus the calculator may not quantify her actual risk for PJI. However, it provides quantitative perspective on the cumulative nature of her various comorbid conditions and their impact on her increased relative risk of PJI. It is my understanding that she was not a Medicaid recipient, and she was therefore not included in a "State Buy-In" insurance plan.

Using TJRRC, I calculated the risks of PJI within two years following TKA in a White woman age 65-69 years and 5'3" tall according to various combinations of Ms. Trombley's comorbid risk factors. In the first calculation I assumed that she was not obese (169 lbs, BMI < 30) and had no other risk factors. In the second calculation I assumed that she was obese (210 lbs, BMI 37.2), but had no other comorbid risk factors. In subsequent calculations, I included increasing numbers of her other comorbidities.

[13] Available at: http://riskcalc.aaos.org/input.html

	Comorbid Conditions	Average Two-Year Risk of PJI
1)	Body weight = 169, BMI = 29.9; No comorbid risk factors	1.06% (95% CI: 0.91-1.23)
2)	Body weight = 210, BMI = 37.2 No other comorbid risk factors	1.55% (95% CI: 1.30-1.86)
3)	Body weight = 210, BMI = 37.2 Diabetes, Hypertension, Hypercholesterolemia	2.27% (95% CI: 1.93-2.68)
4)	Body weight = 210, BMI = 37.2 Diabetes, Hypertension, Hypercholesterolemia, Renal disease, Drug abuse	2.89% (95% CI: 2.34-3.57)
5)	Body weight = 210, BMI = 37.2 Diabetes, Hypertension, Hypercholesterolemia, Renal disease, Drug abuse, Anemia,	3.47% (95% CI: 2.78-4.33)
5)	Body weight = 210, BMI = 37.2 Diabetes, Hypertension, Hypercholesterolemia, Renal disease, Drug abuse, Anemia, Rheumatologic disease UTI	4.52% (95% CI: 3.60-5.66)

19. For perspective, I accessed a second PJI Risk Calculator that was provided as part of the Second International Consensus Meeting on Musculoskeletal Infection (ICM-2). That calculator, based on the work of Tan et al 2018 (14), considered slightly different risk factors and predicted the lifetime risk of PJI:.

	Comorbid Conditions	Estimated Lifetime Risk of PJI
1)	Body weight = 169, BMI = 29; Government insurance; No comorbid risk factors	0.9%
2)	Body weight = 210, BMI = 37 Government insurance; No other comorbid risk factors	1.02%

3)	Body weight = 210, BMI = 37 Government insurance; Diabetes,	1.66%
4)	Body weight = 210, BMI = 37 Government insurance; Diabetes; Renal disease	4.03%
5)	Body weight = 210, BMI = 37 Government insurance; Diabetes; Renal disease; Rheumatologic disease	8.39%
6)	Body weight = 210, BMI = 37 Government insurance; Diabetes; Renal disease; Rheumatologic disease; Drug Abuse	31.46%

20. It can be seen that compared to an otherwise similar person without comorbid risk factors, a level of obesity comparable to Ms. Trombley's significantly increases the relative risk of PJI. With the inclusion of Ms. Trombley's other various comorbid risk factors (i.e., diabetes; renal disease; hypertension; hypercholesterolemia; anemia; rheumatologic disease; drug abuse), the two-year relative risk of PJI would increase by more than 4-fold and the life-time risk of PJI would increase more than 30-fold compared to those of an otherwise similar person without comorbid risk factors.

Thus, it is not simply the individual risk factors, but their combination that explains such a dramatically increased risk of PJI in this case. Likewise, they explain the variability of risk in other patients. Such large risk variations are not related to or explained by the various possible sources of bacteria: they are determined in each case by the patient's underlying condition and comorbid factors.

F. Bair Hugger and Prosthetic Joint Infections

21. In my previous reports and testimony, I opined that there was insufficient evidence that use of Bair Hugger caused increased rates of PJI. I discussed the McGovern study (51), on which Dr. Jarvis now relies, but which is flawed by systematic bias and confounders that were ignored in the analysis. In addition, the surgical infection data presented in McGovern were truncated, internally inconsistent, and incorrectly tabulated. For such reasons, I concluded that that study lacked validity and could not be relied upon as evidence of a significant association.

22. Two recent (2018) peer-reviewed reports by Dr. Mike Reed, senior author of the McGovern study, provide further insight into the limitations of that original study.

22a) The first report, Jeans et al (52), describes the beneficial effects of pre-operative screening and decolonization for methicillin sensitive Staphylococcal aureus (MSSA) in TJA patients treated at three Northumbria Healthcare Trust hospitals, including Wansbeck General Hospital, site of the McGovern study. The results confirm Reed's earlier, less formal report of the benefits of MSSA screening (49). This study confirms that adoption of MSSA screening almost exclusively for patients using the non-BH warmer would have confounded the results of the McGovern study. The Jeans study also demonstrates two other failings of the McGovern study.

22a$_1$) The McGovern study began in July 2008 because, according to Dr. Reed's deposition, surveillance data were incomplete prior to that date [Reed depo p. 63-4]. However, the Jeans report states that there were "complete data available from prior to screening programme (1st January 2007 to 31st December 2009)". Thus, the Jeans study seemingly contradicts that testimony and provides evidence that the dataset used in the McGovern study was arbitrarily truncated.

22a$_2$) An important limitation of the McGovern study was that its analyses were only univariate, thus the effects of confounders were ignored. The Jeans study employed multivariate analyses, indicating that Reed and colleagues recognized the greater statistical meaningfulness of studies that simultaneously consider the impacts of confounding factors.

22b) The second report, Kümin et al (53), described a pilot study for a controlled trial comparing BH and non-BH warming for hip fracture patients undergoing hemi-arthroplasty. Explaining the need for such a study, and in presenting its research design, Reed and his coauthors made the following comments about the McGovern study, further affirming criticisms that I and others have directed at that study:

"An observational study in one hospital over a 2.5-year period suggested that the risk of developing deep infection up to 60 days after surgery was substantially greater for patients treated with FAW than RFW [(53)], but there were significant confounding factors in this study."

23. In addition, Dr. Reed co-authored the ICM-2 recommendation on use of forced air warming (FAW) in orthopedic surgery and PJI. That consensus (93% agreement) found that there was "no evidence to definitively link FAW to an increased risk of SSI/PJIs" (54). Moreover, discussing the McGovern study, the ICM-2 document noted that the McGovern authors:

"did not account for infection control procedures that changed over the study period or account for several possible differences in patient risk factors, such as obesity and fitness for surgery. Other studies of the same cohorts by these researchers revealed potential impacts unrelated to the change in warming modality …" (54)

Thus it is my opinion that there is now even greater reason to discount the McGovern study as biased and unreliable.

24. The lack of probative value of the McGovern study can be seen from another perspective. Despite a burgeoning literature on arthroplasty and PJIs, McGovern remains the only study that purports to present clinical evidence that Bair Hugger is associated with an increased risk of PJI.[14] The significance of the fact that the study is so isolated and has never been replicated is made more obvious by consideration of the actual numbers of published PJI studies. The following graph (adapted from (15)) illustrates the increasing number of PJI studies and reports published between 1982 and 2014.

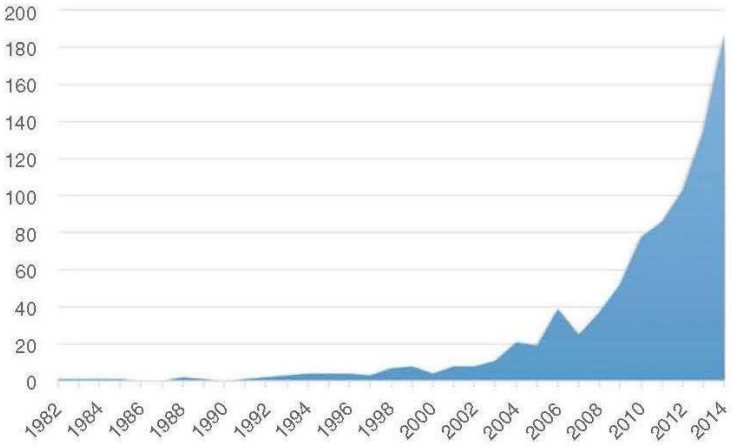

Fig. 5.2 Increasing number of PubMed publications that study PJI each year

adapted from (15)

25. To determine the more recent history of such studies, I accessed PubMed [15] to determine the total numbers of PJI reports published annually from 2014 through 2018:

Table 4: Total PJI Publications by Year of Publication

Year	# of PJI Publications
2014	237
2015	260
2016	326
2017	411
2018	439

[14] There exists a second study (Augustine 2017) that claims to provide such clinical evidence (55). But, as described in my Supplemental Report #2 (11/27/2017), it is neither valid nor reliable, and it lacks integrity. Augustine 2017 repeatedly ignored its stated study design, repeatedly cherry picked data in a way that favored non-FAW over BH, included data from a hospital that never used BH, and included data from hospitals that did not meet inclusion criteria. Notably, Augustine (the author) was also the employer of Mark Albrecht when Mr. Albrecht served as statistician and co-author of the McGovern study.

[15] PubMed is medical literature database system maintained by the US National Library of Medicine.

Thus, despite increasing concerns about the causes of PJI and the accumulation of more than 2140 PJI publications, the McGovern study remains unconfirmed as the only clinical report claiming that use of Bair Hugger is associated with increased rates of PJI.

26. The Jarvis report also alludes to "various case reports" that support his opinion that "Bair Hugger significantly increases risks of PJI," but those case reports are not identified. Moreover, case reports cannot provide evidence of "increased risks of PJI" due to Bair Hugger because they do not provide the sorts of quantitative data necessary to perform such risk calculations. Thus the Jarvis statement is logically inconsistent and statistically without meaning.

27. Accordingly, it is my opinion that there is no valid evidence that use of Bair Hugger increases the risk of PJIs.

G. Report of Dr. Jarvis

28. In his report, Dr. Jarvis states that "the determinative issue is therefore the most likely ***mechanistic source*** of the bacteria that inoculated the joint". His report goes on to consider only a number of possible intraoperative "mechanistic sources" of bacteria. However, it is not correct to assert that source of bacteria was necessarily the determinative factor in this case. His methodological approach ignores other relevant and well-documented factors that are proven to directly contribute to the risk of surgical infections.

29. Dr. Jarvis failed to consider a number of factors other than "mechanistic sources" of bacteria that are of proven relevance to the development of surgical infections (56-59). Following are three examples of causes of infection that are not "mechanistic sources" of inoculation.

29a) Perioperative Hypothermia: One example is maintenance of perioperative normothermia to prevent hypothermia. There is sufficient evidence that warming surgical patients reduces rates of SSI. And, as discussed below, there is also evidence that maintaining normothermia significantly reduces the risks of other important surgical complications. For such reasons, use of perioperative warming has become a standard of current surgical care, recommended by CDC (57) and WHO (58). The ability of maintaining normothermia to prevent surgical infections is related to the adverse effects of hypothermia on blood flow (vasoconstriction) and decreased tissue perfusion, impaired tissue healing, and suppressed immune function (58). I am not aware of any evidence that patient hypothermia is a ***mechanistic source*** of bacteria, yet it can directly increase the risks and rates of surgical infection.

29b) Tissue Oxygenation and Prophylactic Antibiotic Dosing: In my earlier reports, I considered other intraoperative factors that directly contribute to the risks of PJI, but which are not examples of ***mechanistic sources*** of infection. For example, I considered inadequate tissue oxygenation and inadequate dosing of prophylactic

antibiotics. My purpose was to indicate that such factors can and do directly lead to increased risks of infection in surgical patients without being ***mechanistic sources***.

Decreased tissue oxygenation is one of the mechanisms proposed to explain increased rates of surgical infections in patients with diabetes, anemia, obesity and cardiovascular disease. Increased rates of surgical infection in obese patients may also be due to inadequate prophylactic antibiotic dosing, a result of obesity-related effects on the pharmacokinetics of antibiotics. I am not aware of any evidence that inadequate tissue oxygenation or prophylactic dosing is a ***mechanistic source*** of bacteria, yet they can directly increase the risks and rates of surgical infection.

It is notable that Ms. Trombley was obese and that she suffered longstanding anemia.

29c) Immune System Dysfunction: It is generally understood that suppression of normal immune function predisposes to infections including those following surgery. An example of relevance is the increased risks of infectious disease in patients who use corticosteroids. A history of corticosteroid administration is a "Strong Risk Factor" for PJI (8). Two recent meta-analyses found significantly increased risk of PJI associated with preoperative use of corticosteroids (12;60).

Corticosteroids have inhibitory effects on a broad range of immune cells and thereby predispose to a range of infections:

> "Glucocorticoid therapy is a likely mediator [of serious infections] as it impairs phagocyte function and suppresses cell-mediated immunity." (61)

The resulting immune suppression and risk of infection are associated with both the dose and the duration of corticosteroid use (61-63). The following table illustrates the impact of treatment duration when even "low doses" steroids were prescribed to patients with rheumatoid arthritis, a condition for which treatment overlaps that used for psoriatic arthritis.

Table 5: Pattern of Steroid Use and Risks of Serious Infection *

Pattern of Use	Reference Group	Adjusted OR (95% CI)
Current use, 5 mg/day, 7 days	Non-user	1.03 (1.02-1.11)
Current use, 5 mg/day, 28 days	Non-user	1.11 (1.08-1.26)
Current use, 5 mg/day, 3 months	Non-user	1.30 (1.21-1.45)
Current use, 5 mg/day, 6 months	Non-user	1.46 (1.31-1.65)
Current use, 5 mg/day, 1 year	Non-user	1.55 (1.41-1.88)
Current use, 5 mg/day, 3 years	Non-user	2.00 (1.69-2.26)

* Adapted from (61)

These data show that as little as 5 mg of prednisone per day for one week caused a statistically significant increased risk of serious infection, and also that the risk

increased as duration of treatment lengthened. After three years of daily 5 mg doses, and a total cumulative dose of 5475 mg, risk of infection is doubled. It is therefore notable that Ms. Trombley was prescribed a total of 9660 mg of prednisone over a span less than two years [16WA:-00008-00047], with a daily dose rate that averaged more than 10 mg per day. Accordingly, it is reasonable to expect that Ms. Trombley was immunosuppressed and at increased risk of infection because of her use of prednisone. I find no objective basis for Dr. Jarvis' opinion that Ms. Trombley's "dosage of prednisone would not be immunosuppressive" and also no basis for ignoring the role of immunosuppression in her case.

Abnormalities of the immune system, whether due to corticosteroids or other medical conditions, such as diabetes, thyroid dysfunction or AIDS, are not ***mechanistic sources*** of bacteria, although they are important risk factors for infection.

30. Thus, it is my opinion that Dr. Jarvis ignored important factors that have been repeatedly shown to directly contribute to surgical site infections, choosing to focus solely on "***mechanistic sources***". It is of particular relevance that he ignored the importance of obesity, diabetes, anemia, hypertension, hypercholesterolemia, CKD, and chronic steroid use to the development of Ms. Trombley's post-operative infection.

31. In addition, Dr. Jarvis considered only intraoperative sources of infection, focusing on preoperative procedures, OR procedures, and staff behaviors during Ms. Trombley's surgery. As I have previously discussed, it is well recognized that PJI can result from post-operative exposures including bacterial entry at the surgical site or blood-borne bacterial seeding. It is my opinion that Dr. Jarvis had no objective basis for concluding that Ms. Trombley's infection was specifically due to intraoperative inoculation of the wound.

32. With regards to his narrow focus on intraoperative sources of infection, Dr. Jarvis opined that the "surgical procedures and techniques can be ruled out as a likely cause" of Ms. Trombley's infection. That statement is not consistent with the opinions of Dr. Reed, the senior author of the McGovern study. In 2015, Dr. Reed wrote that:

"Contaminants may arise from the patient' skin, from the surgical personnel or from the surgical instrumentation itself. It is likely that almost all surgical wounds are contaminated because skin preparation at the time of surgery will only decontaminate the skin surface and bacteria will remain in deeper layers of the skin" (49).

33. Dr. Jarvis also concluded that he could "properly" rule out infection attributable to Ms. Trombley's own flora because of the skin preparation performed preoperatively, and because she "had no evidence of any gastrointestinal or genitourinary tract issues". However, there is no scientific basis for that opinion.

33a) First, Dr. Jarvis acknowledged that the skin preparation would not fully eliminate all skin flora. The same opinion was expressed by Dr. Beer, who

discussed preoperative skin preparation during his deposition. He testified that it would not sterilize the skin:

> Q. … would you agree the purpose of it is to reduce the bacteria?
> A To reduce the bacteria count.
> Q So you're reducing the burden?
> A Yeah.
> Q But not 100 percent?
> A I don't think it's 100 percent. [Beer depo p.51-2]

33b) Moreover, as Dr. Jarvis wrote in his report, GBS is an uncommon skin colonizer. Thus his focus on the adequacy of Ms. Trombley's preoperative skin preparation is insufficient to rule out infection attributable to her own flora. To the contrary, there are robust data that GBS colonize the rectum, perianal area, vagina, urethra, and only "less commonly … skin and pharynx" (33;64;65). Colonization by GBS has been documented in about 22% of "healthy, ambulatory" older adults by means of rectal swabs, vaginal swabs and urine samples (64). Over all, studies report colonization rates that range from 20-35% (33).

Dr. Jarvis also apparently concluded that Ms. Trombley was not colonized by GBS because she had "no evidence of any gastrointestinal or genitourinary tract issues". However, the vast majority of the colonized adults discussed above were healthy and asymptomatic (i.e., they had no such "issues").

In addition, Dr. Jarvis ruled out her urinary tract as a source of her infection because "subsequently, as part of her nephrology evaluation, she had a urine culture and it was not positive for GBS". However, he ignored that Ms. Trombley had reported a history of "recurrent urinary tract infections" and that the negative urine culture was obtained after a six-week course of ceftriaxone followed by oral cephalexin [24-NCNWO-00005]. Thus the negative urine culture provided no insight into whether Ms. Trombley was colonized with GBS at the time of her surgery.[16]

33c) Dr. Jarvis also ignored an extensive literature documenting that "bacteremia without an identified source" is a common clinical presentation of GBS infection, representing 15-42% of non-pregnant adult patients with invasive GBS infections (29;30;33;66-68). In other words, a substantial proportion of GBS infections result from hematogenous spread and blood-borne bacterial seeding.

Thus I find no objective basis for Dr. Jarvis' opinion that "Ms. Trombley's own flora can be properly ruled out" and no basis to rule out blood-borne bacterial seeding as the source of her PJI.

34. Furthermore, Dr. Jarvis concluded "based on my review of the medical records" that staff followed appropriate standards of care and that there was "no evidence" of any break in the sterile field. However, there is evidence that violations of OR antisepsis

[16] I found no evidence in the records that her urine was sterile at the time of her surgery in 12/11.

protocols occur with surprising frequency, even with well-trained university-based OR staff.

I previously discussed the findings from a Swiss university hospital that monitored compliance with OR antisepsis protocols by assigning "experienced" nurses to observe the behavior of OR staff during surgery (69). In that study, one or more protocol violations occurred in 66.2% of cases; three or more violations occurred in 25.1%. One or more violations was associated with a more than doubling of the surgical infection rate (OR: 2.02, 95% CI: 1.05-3.88, $p = 0.04$). The occurrence of such protocol violations does not necessarily imply deviations from standards of care: "standards of care" do not imply perfection.[17] It seems that strict adherence to intraoperative antisepsis protocols, even in university hospitals, is the exception.

Thus it is my opinion that Dr. Jarvis could not rule out "surgical procedures and techniques" as a "likely cause" of Ms. Trombley's infection simply because, based on his review of the written records, "the surgical procedure and technique were within the standard of care."

35. Also in his report, Dr. Jarvis states that "a relative risk of 2.0 in and of itself shows that the device or drug at issue is the most likely cause of the disease". That statement is fundamentally wrong. While it is correct to say that a relative risk ≥ 2 indicates that the specific association in the specific context is more likely than not true (i.e., not due to chance), it does not mean that the association is causal. In my previous reports, I provided several examples to illustrate the error of Dr. Jarvis' statement. I also provided an example to illustrate that each of multiple risk factors could simultaneously have relative risks ≥ 2.0. Thus, reliance on the RR alone, "in and of itself," could not differentiate among alternative potential causes of infection.

36. Dr. Jarvis relied on a relative risk value derived from the McGovern study to conclude causation. Over and beyond that study's methodological flaws, that relative risk value was determined using only a univariate analysis. Because such analyses ignore other potential causes and confounders, reliance solely on that calculated value also ignored other potential causes and confounders. In fact, the McGovern study did not evaluate other potential causes. In addition, the study findings have not been replicated in a valid study.

37. Thus it is my opinion that Dr. Jarvis could not rely solely on the McGovern study and its calculated relative risk as the basis for concluding that Bair Hugger causes infections.

38. In addition to the McGovern study, Dr. Jarvis relied on a combination of particle-related studies to support his opinion that Bair Hugger caused Ms. Trombley's infection:

[17] **"**Medical Definition of Standard of care: … the level at which the average, prudent provider in a given community would practice. It is how similarly qualified practitioners would have managed the patient's care under the same or similar circumstances."
https://www.medicinenet.com/script/main/art.asp?articlekey=33263

> "The McGovern study and/or Dr. Elghobashi's CFD model paired with the Stocks and Darouiche studies each independently confirm that the Bair Hugger is the most likely cause of Mrs. Trombley's PJI." [Report p.11]

I have earlier described the clinical component of the McGovern study and the reasons that it "does not independently confirm" that Bair Hugger caused her infection. A second component of that study involved use of "neutrally buoyant detergent bubbles" to visualize airflow patterns in an OR during simulated surgery, comparing two different warming devices, Bair Hugger vs. a device manufactured by Augustine Temperature Management. The bubbles were 4 mm (4000 μm) in diameter. The study reported that more bubbles were visualized over the "surgical site" when Bair Hugger was used.

The bubble component of the McGovern study did not consider bacteria and it did not consider infections. As discussed below, it also did not consider particles comparable in size or composition to those of the Elghobashi, Stocks and Darouiche studies. Accordingly, it does not "independently confirm" that Bair Hugger is the most likely cause of Ms. Trombley's infection and when "paired with" the Elghobashi and/or Stocks and Darouiche studies, it does not confirm that Bair Hugger is the most likely cause of Ms. Trombley's infection. An additional source of concern is the possibility of bias introduced by the fact that this component of the McGovern study was directed by Mr. Mark Albrecht, then an employee of Augustine Temperature Management.

Following is a discussion of the Elghobashi, Stocks and Darouiche studies, as well as several other "particle-related" studies, indicating that such studies also do not confirm, either "independently" or in conjunction, that Bair Hugger caused Ms. Trombley's infection.

> **38a**) The Elghobashi study (70) is a computer simulation ("large eddy simulation") of hypothetical exposures in an imaginary OR ("The CAD model simulated a realistic OR … [it] also includes several items that are usually present in a real OR"). The model was used to calculate the probable distributions of shed skin cells placed on the floor of an OR that might reach "the surgical site … 4 imaginary boxes of interest"). The study did not include any actual patients or surgeries, it did not consider actual particles, and it did not consider PJIs. The hypothetical particles considered in the study had aerodynamic diameters of exactly 10 μm, although the authors noted that particles of theoretical concern actually range from 4 to 20 μm. (By contrast, the McGovern bubble study used 4000 μm "particles", 200- to 1000-fold greater than the range of "theoretical concern".) In concluding, the authors agreed that the study was not based on "detailed experimental measurements … in an OR during a clinical trial" and that there was need for real world studies to validate their findings.

Accordingly, the relevance of this not-yet-validated, hypothetical simulation to the actual infection suffered by Ms. Trombley is uncertain and not obvious.

38b) The Stocks study (71) involved simultaneous collection of 10-minute air samples during orthopedic procedures and their analysis for airborne particles (6 bins categorized by diameter) and colony forming units (CFUs, a measure of viable bacteria). The key concern was the relationship between particle number and CFU number. The analyses included "bivariate" regression and multivariate regression.

The bivariate regressions indicated significant positive relationships between CFU number and particle number for 5-9.9 µm and ≥10 µm particles, but not for smaller particles.[18] While significant, the effect of the 5-9.9 µm particles was less than 5% that of the ≥10 µm particles. Multivariate analyses indicate that only the ≥10 µm particles were positively and significantly related to CFU counts. In a model that included both 5-9.9 µm and ≥10 µm particles, the parameter for 5-9.9 µm particles was highly significant and negative (p = 0.001).[19] These results indicate that the apparent positive association of CFU and 5-9.9 µm particles was due to confounding. Moreover, they suggest a possible significant negative relationship between the number of 5-9.9 µm particles and CFU count. In other words, the multivariate analyses suggest that increased 5-9.9 µm particle counts might protect against bacterial contamination. (Stocks did not consider particles ≥4000 µm (or 4mm), the size of the McGovern bubbles).

The relevance of Stocks to either general questions about Bair Hugger or specific questions about Ms. Trombley is not obvious. First, Stocks did not study Bair Hugger and none of the study patients developed "clinical signs or symptoms of infection". Second, as detailed below, I am not aware of any studies documenting increased numbers of airborne particles ≥10 µm (other than McGovern's 4000 µm detergent bubbles) as a result of Bair Hugger.

38b$_1$) Legg et al (72) tested Bair Hugger in an actual OR in which a volunteer was positioned on an operating table and a surgeon simulated TKA surgery, but no nurses were employed. The numbers of particles, according to three bins (0.3 µm, 0.5 µm, and 5.0 µm), were counted over the "surgical site" five times during the mock procedure. Compared to no warming, particles counts were significantly increased with Bair Hugger, but 99.7% of particles were <5.0 µm. No data were determined for particles >5 µm. (Note that Stocks reported that particles of the size counted in this study were not association with CFU counts).

38b$_2$) Legg and Hamer (73) replicated the experimental conditions of their prior study using artificial smoke ("glycerol tracer particles") to visualize air flows during simulated surgery using Bair Hugger. However, the particles they used were 0.3 µm in diameter. No information was provided about larger particles. (Note that Stocks reported that particles of the size used in this study were not association with CFU counts).

[18] The analyses actually considered the square root transformation of the CFU count.

[19] Regression parameters indicate the direction and magnitude of the effect of each specific variable on the outcome of concern.

38b$_3$) McGovern et al [McGovern depo exhibit 6, 01/04/17][20] described an experiment in an actual OR in which a volunteer was positioned on an operating table and surgery was simulated. The numbers of airborne particles, according to three bins (0.3 µm, 0.5 µm, and 5.0 µm), were counted over the "surgical site" during use of Bair Hugger. The study found "no notable increase in … ambient particle count when a forced air warming device is being used."

In summary, the Stocks study did not consider Bair Hugger and its results are not relevant to the size of particles that have been associated with use of Bair Hugger. Thus, the Stocks findings seem unrelated to the documented effects of Bair Hugger and they are not directly relevant to the infection suffered by Ms. Trombley.

38c) Darouiche et al (74) performed a random control trial of an "air barrier system" to reduce particle counts over the surgical site during various procedures. Half of the patients underwent THA; the others had spinal or vascular procedures. The authors did not indicate whether BH was used during these procedures. Numbers of particles (0.3 µm, 0.5 µm, 1 µm, 5 µm and ≥10 µm) and numbers of CFU were measured during the first 100 minutes of each case. Use of the barrier significantly reduced the number of total particulates and CFU, but results were not provided according to particle size. CFU count was significantly associated with deep, but not with incisional infections; that association was not reported by particle size. A series of sub-analyses considered relationships between particle number grouped by size, CFU number, and specific risk factors: In the controls (i.e., no barrier), there were no significant associations between CFU count and particles ≥10 µm. (By contrast, Stocks reported a significant association between CFU count and particles ≥10 µm, while the McGovern bubble study used only "particles" ≥4000 µm.)

Because this study did not directly consider Bair Hugger, and because it did not report significant associations between CFU count and particles ≥10 µm, it is not obvious that Darouiche provides support for the Stocks study. Likewise, it is not obvious that Darouiche is directly relevant to the infection suffered by Ms. Trombley.

38d) Oguz et al 2017 (75) determined the CFU counts on six collection points at "standardized locations in the OR" during 80 orthopedic procedures, 40 using BH and 40 using non-FAW. The type of warming system had "no significant influence on bacterial counts on any sampling site".

The differences in the sizes of particles considered in the above studies are not merely analytical distinctions: they have real world importance. As emphasized by Elghobashi, and first described by Noble in 1964 (76), particles that carry bacteria are in the range of 4 to 20 µm. Thus, the particles that have been experimentally associated with use of Bair Hugger are too small to carry bacteria.

[20] McGovern PD et al: Do forced air warming devices increase bacterial contamination of operative field? – Simulated experiment analysis [Unpublished manuscript]. McGovern depo exhibit 6: 01/05/17.

39. Thus it is my opinion that Dr. Jarvis could not rely on the bubble component of the McGovern study and/or the Elghobashi, Stocks and Darouiche studies as the basis for concluding that Bair Hugger causes infections.

H. Hypothermia and Other Surgical Complications

40. The discussion above largely focused on risk factors, including hypothermia, that have been associated with increased risk of surgical infections. It might wrongly be inferred that the reason for using Bair Hugger is solely to prevent infections. To the contrary, there is evidence that perioperative hypothermia is associated with a variety of important surgical complications other than infection. This was well summarized in a 2013 report by Leijtens et al (77):

> "Inadvertent hypothermia is an important complication of major surgery. Even mild peri-operative hypothermia can cause a variety of adverse effects (78), such as: morbid myocardial events (79), increased risk of surgical peri-prosthetic infections, increased duration of hospitalization (80-82), intra-operative blood loss (83;84) and prolonged postanesthetic recovery (80). These effects can be considerable, a decrease of 1.9 °C in core temperature triples the relative risk of surgical peri-prosthetic infection and increases the duration of hospitalization by 20% (80;82)."

For such reasons, use of perioperative warming has become a standard of current surgical care, recommended by CDC (57) and WHO (58).

I. Summary

41. Following is a list of my opinions, all to a reasonable degree of medical and scientific certainty.

41a) There is no valid evidence that use of Bair Hugger increases the risk of PJIs. Accordingly, there is no basis to conclude that use of Bair Hugger "is the most likely cause of Ms. Trombley's PJI."

41b) There is no objective basis for concluding that Ms. Trombley's infection was due to intraoperative inoculation of the wound.

41c) Ms. Trombley's obesity was a risk factor that directly contributed to her development of PJI.

41d) Ms. Trombley's diabetes was a risk factor that directly contributed to her development of PJI.

41e) Ms. Trombley's use of opioid medications was a risk factor that directly contributed to her development of PJI.

41f) Ms. Trombley's chronic anemia was a risk factor that directly contributed to her development of PJI.

41g) Ms. Trombley's chronic kidney disease was a risk factor that directly contributed to her development of PJI.

41h) Ms. Trombley's hypertension and hypercholesterolemia were risk factors that directly contributed to her development of PJI.

41i) Ms. Trombley's psoriatic arthritis (and presumably underlying psoriatic skin disease) directly contributed to her development of PJI.

42. I reserve the right to amend my report and opinions should further information become available.

I declare under penalty of perjury that the foregoing is true and correct

Jonathan Borak, MD, FACP, FACOEM

February 14, 2019

Reference List

(1) Centers for Disease Control and Prevention (CDC). Growth Chart Training: Calculating BMI Using the English System (https://www.cdc.gov/nccdphp/dnpao/growthcharts/training/bmiage/page5_2.html). Atlanta: U.S. Department of Health & Human Services, Centers for Disease Control and Prevention (CDC); 2014.

(2) Jamsa PP, Oksala NK, Eskelinen AP, Jamsen ER. Chronic kidney diseases among patients undergoing elective arthroplasty: Risk groups and the value of serum creatinine. J Arthroplasty 2018; 33:230-234.

(3) Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med 2002; 162:1401-1408.

(4) El-Achkar TM, Ohmit SE, McCullough PA, Crook ED, Brown WW, Grimm R et al. Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program. Kidney Int 2005; 67:1483-1488.

(5) Hsu C-Y, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol 2002; 13:504-510.

(6) Gauci R, Hunter M, Bruce DG, Davis WA, Davis TME. Anemia complicating type 2 diabetes: Prevalence, risk factors and prognosis. J Diabetes Complications 2017; 31:1169-1174.

(7) Rosenberg M, Curhan GC, Motwani S. Overview of the management of chronic kidney disease in adults (https://www.uptodate.com/contents/overview-of-the-management-of-chronic-kidney-disease-in-adults). Uptodate, Inc.; 2019.

(8) Kunutsor S, Iorio R, Feng JE, Cizmic Z. What modifiable and non-modifiable host factors contribute to an increased risk of surgical site infection/periprosthetic j oint infections (SSIs/PJIs)? Proceedings of the Second International Consensus Meeting (ICM) on Musculoskeletal Infection (General Assembly). Brooklandville: Data Trace Publishing Company; 2018. 15-19.

(9) Haverkamp D, Klinkenbijl MN, Somford MP, Albers GH, van der Vis HM. Obesity in total hip arthroplasty--does it really matter? A meta-analysis. Acta Orthop 2011; 82:417-422.

(10) Liu W, Wahafu T, Cheng M, Cheng T, Zhang Y, Zhang X. The influence of obesity on primary total hip arthroplasty outcomes: A meta-analysis of prospective cohort studies. Orthop Traumatol Surg Res 2015; 101:289-296.

(11) Kerkhoffs GM, Servien E, Dunn W, Dahm D, Bramer JA, Haverkamp D. The influence of obesity on the complication rate and outcome of total knee arthroplasty: a meta-analysis and systematic literature review. J Bone Joint Surg Am 2012; 94:1839-1844.

(12) Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD. Patient-related risk factors for periprosthetic joint infection after total joint arthroplasty: A systematic review and meta-analysis. PloS One 2016; 11(3):e0150866.

(13) George J, Piuzzi NS, Ng M, Sodhi N, Khlopas AA, Mont MA. Association between body mass index and thirty-day complications after total knee arthroplasty. J Arthroplasty 2018; 33:865-871.

(14) Tan TL, Maltenfort MG, Chen AF, Shahi A, Higuera CA, Siqueira M et al. Development and evaluation of a preoperative risk calculator for periprosthetic joint infection following total joint arthroplasty. J Bone Joint Surg Am 2018; 100:777-785.

(15) Tan TL, Kheir MM, Chen AF. Who is at Risk for Periprosthetic Joint Infection? In: Kendoff D, Morgan-Jones R, Haddad FS, editors. Periprosthetic Joint Infections. Changing Paradigms. Swizerland: Springer; 2016. 61-75.

(16) Bozic KJ, Lau E, Kurtz S, Ong K, Rubash H, Vail TP et al. Patient-related risk factors for periprosthetic joint infection and postoperative mortality following total hip arthroplasty in Medicare patients. J Bone Joint Surg Am 2012; 94:794-800.

(17) Bozic KJ, Lau E, Kurtz S, Ong K, Berry DJ. Patient-related risk factors for postoperative mortality and periprosthetic joint infection in medicare patients undergoing TKA. Clin Orthop Relat Res 2012; 470:130-137.

(18) Lenguerrand E, Whitehouse MR, Beswick AD, Kunutsor SK, Burston B, Porter M et al. Risk factors associated with revision for prosthetic joint infection after hip replacement: a prospective observational cohort study. Lancet Infect Dis 2018; 18:1004-1014.

(19) Bell KL, Shohat N, Goswami K, Tan TL, Kalbian I, Parvizi J. Preoperative opioids increase the risk of periprosthetic joint infection after total joint arthroplasty. J Arthroplasty 2018; 33:3246-3251.

(20) Yang Z, Liu H, Xie X, Tan Z, Qin T, Kang P. The influence of diabetes mellitus on the post-operative outcome of elective primary total knee replacement: a systematic review and meta-analysis. Bone Joint J 2014; 96-B:1637-1643.

(21) Soohoo NF, Farng E, Lieberman JR, Chambers L, Zingmond DS. Factors that predict short-term complication rates after total hip arthroplasty. Clin Orthop Relat Res 2010; 468:2363-2371.

(22) Jamsen E, Nevalainen P, Eskelinen A, Huotari K, Kalliovalkama J, Moilanen T. Obesity, diabetes, and preoperative hyperglycemia as predictors of periprosthetic joint infection: a single-center analysis of 7181 primary hip and knee replacements for osteoarthritis. J Bone Joint Surg Am 2012; 94:e101-1-e101-9.

(23) Pedersen AB, Mehnert F, Johnsen SP, Sorensen HT. Risk of revision of a total hip replacement in patients with diabetes mellitus: a population-based follow up study. J Bone Joint Surg Br 2010; 92:929-934.

(24) Iorio R, Williams KM, Marcantonio AJ. Diabetes mellitus, hemoglobin A1C, and the incidence of total joint arthroplasty infection. J Arthroplasty 2018; 27:726-729.

(25) American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes--2018. Diabetes Care 2018; 41 (suppl 1):S13-S27.

(26) Harris AH, Bowe TR, Gupta S, Ellerbe LS, Giori NJ. Hemoglobin A1C as a marker for surgical risk in diabetic patients undergoing total joint arthroplasty. J Arthroplasty 2013; 28 (Suppl 8):25-29.

(27) Chrastil J, Anderson MB, Stevens V, Anand R, Peters CL, Pelt CE. Is Hemoglobin A1c or Perioperative Hyperglycemia Predictive of Periprosthetic Joint Infection or Death Following Primary Total Joint Arthroplasty? J Arthroplasty 2015; 30:1197-1202.

(28) Maradit Kremers H, Lewallen LW, Mabry TM, Berry DJ, Berbari EF, Osmon DR. Diabetes mellitus, hyperglycemia, hemoglobin A1C and the risk of prosthetic joint infections in total hip and knee arthroplasty. J Arthroplasty 2015; 30:439-443.

(29) Schwartz B, Schuchat A, Oxtoby MJ, Cochi SL, Hightower A, Broome CV. Invasive group B streptococcal disease in adults. A population-based study in metropolitan Atlanta. J Am Med Assoc 1991; 266:1112-1114.

(30) Farley MM, Harvey RC, Stull T, Smith JD, Schuchat A, Wenger JD et al. A population-based assessment of invasive disease due to group B Streptococcus in nonpregnant adults. NEJM 1993; 328:1807-1811.

(31) Nolla JM, Gomez-Vaquero C, Corbella X, Ordonez S, Garcia-Gomez C, Perez A et al. Group B streptococcus (Streptococcus agalactiae) pyogenic arthritis in nonpregnant adults. Medicine (Baltimore) 2003; 82:119-128.

(32) Skoff TH, Farley MM, Petit S, Craig AS, Schaffner W, Gershman K et al. Increasing burden of invasive group B streptococcal disease in nonpregnant adults, 1990-2007. Clin Infect Dis 2009; 49:85-92.

(33) Sendi P, Johansson L, Norrby-Teglund A. Invasive group B Streptococcal disease in non-pregnant adults : a review with emphasis on skin and soft-tissue infections. Infection 2008; 36:100-111.

(34) Goodnough LT, Maniatis A, Earnshaw P, Benoni G, Beris P, Bisbe E et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth 2011; 106:13-22.

(35) Myers E, O'Grady P, Dolan AM. The influence of preclinical anaemia on outcome following total hip replacement. Arch Orthop Trauma Surg 2004; 124:699-701.

(36) Conlon NP, Bale EP, Herbison GP, McCarroll M. Postoperative anemia and quality of life after primary hip arthroplasty in patients over 65 years old. Anesth Analg 2008; 106:1056-1061.

(37) Greenky M, Gandhi K, Pulido L, Restrepo C, Parvizi J. Preoperative anemia in total joint arthroplasty: is it associated with periprosthetic joint infection? Clin Orthop Relat Res 2012; 470:2695-2701.

(38) Tan TL, Kheir MM, Tan DD, Filippone EJ, Tischler EH, Chen AF. Chronic kidney disease linearly predicts outcomes after elective total joint arthroplasty. J Arthroplasty 2016; 31 (suppl 9):S175-S179.

(39) Deegan BF, Richard RD, Bowen TR, Perkins RM, Graham JH, Foltzer MA. Impact of chronic kidney disease stage on lower-extremity arthroplasty. Orthopedics 2014; 37:e613-e618.

(40) McCleery MA, Leach WJ, Norwood T. Rates of infection and revision in patients with renal disease undergoing total knee replacement in Scotland. J Bone Joint Surg Br 2010; 92:1535-1539.

(41) Erkocak OF, Yoo JY, Restrepo C, Maltenfort MG, Parvizi J. Incidence of infection and inhospital mortality in patients With chronic renal failure after total joint arthroplasty. J Arthroplasty 2016; 31:2437-2441.

(42) Mirici A, Inacio MC, Namba RS. Can total knee arthroplasty be safely peformed in patients with chronic renal disease? An evaluation of perioperative morbidity in 2,686 procedures from a Total Joint Replacement Registry. Acta Orthop 2014; 85:71-78.

(43) Sacerdote P. Opioids and the immune system. Palliat Med 2006; 20 (suppl 1):s9-s15.

(44) Sacerdote P. Opioid-induced immunosuppression. Curr Opin Support Palliat Care 2008; 2:14-18.

(45) Odunayo A, Dodam JR, Kerl ME, DeClue AE. Immunomodulatory effects of opioids. J Vet Emerg Crit Care (San Antonio) 2010; 20:376-385.

(46) Menendez ME, Ring D, Bateman BT. Preoperative opioid misuse is associated with increased morbidity and mortality after elective orthopaedic surgery. Clin Orthop Relat Res 2015; 473:2402-2412.

(47) Cozowicz C, Olson A, Poeran J, Morwald EE, Zubizarreta N, Girardi FP et al. Opioid prescription levels and postoperative outcomes in orthopedic surgery. Pain 2017; 158:2422-2430.

(48) Cancienne JM, Patel KJ, Browne JA, Werner BC. Narcotic use and total knee arthroplasty. J Arthroplasty 2018; 33:113-118.

(49) Refaie R, Jameson S, Reed M. Prevention of periprosthetic joint infection. J Trauma Ortho 2015; 3:50-52.

(50) Birgand G, Toupet G, Rukly S, Antoniotti G, Deschamps MN, Lepelletier D et al. Air contamination for predicting wound contamination in clean surgery: A large multicenter study. Am J Infect Control 2015; 43:516-521.

(51) McGovern PD, Albrecht M, Belani KG, Nachtsheim C, Partington PF, Carluke I et al. Forced-air warming and ultra-clean ventilation do not mix: an investigation of theatre ventilation, patient warming and joint replacement infection in orthopaedics. J Bone Joint Surg Br 2011; 93:1537-1544.

(52) Jeans E, Holleyman R, Tate D, Reed M, Malviya A. Methicillin sensitive staphylococcus aureus screening and decolonisation in elective hip and knee arthroplasty. J Infect 2018; 77:405-409.

(53) Kumin M, Harper CM, Reed M, Bremner S, Perry N, Scarborough M. Reducing Implant Infection in Orthopaedics (RIIiO): a pilot study for a randomised controlled trial comparing the influence of forced air versus resistive fabric warming technologies on postoperative infection rates following orthopaedic implant surgery in adults. Trials 2018; 19:640.

(54) Aalirezaie A, Akkaya M, Barnes CL, Bengoa F, Bozkurt M, Cichos KH et al. General assembly, prevention, operating room environment: Proceedings of International Consensus on Orthopedic Infections. J Arthroplasty 2019; 34 (Suppl 2):S105-S115.

(55) Augustine SD. Forced-air warming discontinued: periprosthetic joint infection rates drop. Orthop Rev 2017; 9 (6998):39-42.

(56) Anderson DJ, Podgorny K, Berrios-Torres SL, Bratzler DW, Dellinger EP, Greene L et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014; 35 (suppl 2):S66-S88.

(57) Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg 2017; 152:784-791.

(58) Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F et al. New WHO recommendations on intraoperative and postoperative measures for

surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis 2016; 16:e288-e303.

(59) Dellinger EP, Hausmann SM, Bratzler DW, Johnson RM, Daniel DM, Bunt KM et al. Hospitals collaborate to decrease surgical site infections. Am J Surg 2005; 190:9-15.

(60) Zhu Y, Zhang F, Chen W, Liu S, Zhang Q, Zhang Y. Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. J Hosp Infect 2015; 89:82-89.

(61) Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis 2012; 71:1128-1133.

(62) Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis 1989; 11:954-963.

(63) Ginzler E, Diamond H, Kaplan D, Weiner M, Schlesinger M, Seleznick M. Computer analysis of factors influencing frequency of infection in systemic lupus erythematosus. Arthritis Rheum 1978; 21:37-44.

(64) Edwards MS, Rench MA, Palazzi DL, Baker CJ. Group B streptococcal colonization and serotype-specific immunity in healthy elderly persons. Clin Infect Dis 2005; 40:352-357.

(65) Kaplan EL, Johnson DR, Kuritsky JN. Rectal colonization by group B beta-hemolytic streptococci in a geriatric population. J Infect Dis 1983; 148:1120.

(66) Farley MM. Group B streptococcal infection in older patients. Spectrum of disease and management strategies. Drugs Aging 1995; 6:293-300.

(67) Ho CM, Chi CY, Ho MW, Chen CM, Liao WC, Liu YM et al. Clinical characteristics of group B streptococcus bacteremia in non-pregnant adults. J Microbiol Immunol Infect 2006; 39:396-401.

(68) Edwards MS, Baker CJ. Group B streptococcal infections in elderly adults. Clin Infect Dis 2005; 41:839-847.

(69) Beldi G, Bisch-Knaden S, Banz V, Muhlemann K, Candinas D. Impact of intraoperative behavior on surgical site infections. Am J Surg 2009; 198:157-162.

(70) He X, Karra S, Pakseresht P, Apte SV, Elgobashi S. Effect of heated-air blanket on the dispersion of squames in an operating room. Int J Numer Meth Biomed Engeng 2018; 34:e2960.

(71) Stocks GW, Self SD, Thompson B, Adame XA, O'Connor DP. Predicting bacterial populations based on airborne particulates: A study performed in nonlaminar flow operating rooms during joint arthroplasty surgery. Am J Infect Control 2010; 38:199-204.

(72) Legg AJ, Cannon T, Hamer AJ. Do forced air patient-warming devices disrupt unidirectional downward airflow? J Bone Joint Surg Br 2012; 94:254-256.

(73) Legg AJ, Hamer AJ. Forced-air patient warming blankets disrupt unidirectional airflow. Bone Joint J 2013; 95-B:407-410.

(74) Darouiche RO, Green DM, Harrington MA, Ehni BL, Kougias P, Bechara CF et al. Association of Airborne Microorganisms in the Operating Room With Implant Infections: A Randomized Controlled Trial. Infect Control Hosp Epidemiol 2017; 38:3-10.

(75) Ridker PM. Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: implications for longevity. Nutr Rev 2007; 65:S253-S259.

(76) Noble WC, Lidwell OM, Kingston D. The size distribution of airborne particles carrying micro-organisms. J Hyg (London) 1963; 61:385-391.

(77) Leijtens B, Koeter M, Kremers K, Koeter S. High incidence of postoperative hypothermia in total knee and total hip arthroplasty: a prospective observational study. J Arthroplasty 2013; 28:895-898.

(78) Reynolds L, Beckmann J, Kurz A. Perioperative complications of hypothermia. Best Pract Res Clin Anaesthesiol 2008; 22:645-657.

(79) Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. J Am Med Assoc 1997; 277:1127-1134.

(80) Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. NEJM 1996; 334:1209-1215.

(81) Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomised controlled trial. Lancet 2001; 358:876-880.

(82) Kurz A. Thermal care in the perioperative period. Best Pract Res Clin Anaesthesiol 2008; 22:39-62.

(83) Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. Lancet 1996; 347:289-292.

(84) Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative hypothermia on blood loss and transfusion requirement. Anesthesiology 2008; 108:71-77.